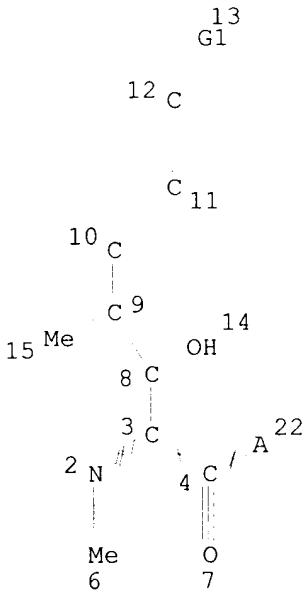
Liu, S
09/976219

(FILE 'REGISTRY' ENTERED AT 14:31:18 ON 07 JAN 2003)

L12 STR



STV.
(A1 + A2)

VAR G1=CY/17/20
REP G2=(0-8) C
NODE ATTRIBUTES:
NSPEC IS RC AT 2
NSPEC IS RC AT 22
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L14 7 SEA FILE=REGISTRY SSS FUL L12

100.0% PROCESSED 247219 ITERATIONS 7 ANSWERS
SEARCH TIME: 00.00.12

FILE 'HCAPLUS' ENTERED AT 15:31:47 ON 07 JAN 2003
L15 6 S L14

L15 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:475261 HCAPLUS
DOCUMENT NUMBER: 121:75261
TITLE: Human Cyclophilin C: Primary Structure, Tissue Distribution, and Determination of Binding Specificity for Cyclosporins
AUTHOR(S): Schneider, Helmut; Charara, Nadine; Schmitz, Rita; Wehrli, Susi; Mikol, Vincent; Zurini, Mauro G. M.; Quesniaux, Valerie F. J.; Movva, N. Rao
CORPORATE SOURCE: Sandoz Pharma Ltd., Basel, CH-4002, Switz.
SOURCE: Biochemistry (1994), 33(27), 8218-24

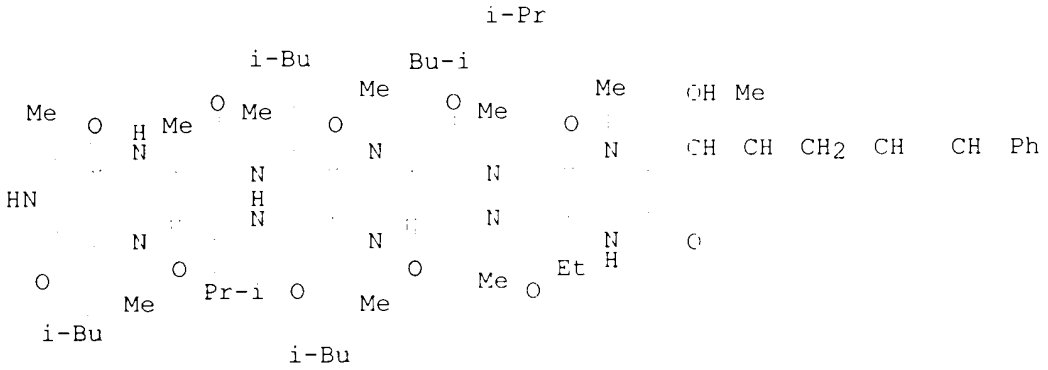
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A cDNA for human cyclophilin C (Cyp-C) was isolated from a human kidney cDNA library. Northern blot expts. with several human tissues and cell lines revealed that Cyp-C is less abundant than Cyp-A. The amt. of Cyp-C mRNA was 10-fold lower than that of Cyp-A in kidney. Expression of human Cyp-C in the kidney is not significantly elevated compared to pancreas, skeletal muscle, heart, lung, and liver. This argues against a previously postulated specific role for Cyp-C in the nephrotoxic effects of CsA in humans, based on the studies of its relative abundance in murine kidney. It is present in extremely low concns. in brain and in the Jurkat T cell line. The binding of recombinant human Cyp-A, -B, and -C to cyclosporin A (CsA) was studied by immunochem. methods. The relative affinity of Cyp-C for CsA is lower by a factor of 2 than that of Cyp-A, which itself is 10-fold lower than that of Cyp-B. Cross-reactivity studies with a series of Cs derivs. showed that Cyp-C binds CsA with a fine specificity similar to that of Cyp-A and Cyp-B. Cs amino acid residues 1, 2, 10, and 11 seemed essential for the interaction with all three Cyp subtypes. However, Cyp-C tolerates a greater variety of structures on Cs position 2 than Cyp-A does, suggesting that this residue of CsA might not be in tight contact with Cyp-C. This was confirmed by modeling of human Cyp-C on the structure of the complex formed by Cyp-A and CsA. The knowledge of the fine specificity of human Cyps for CsA and of their expression levels may provide better insights into how CsA acts on its different target proteins in vivo.

IT **126374-37-6**
RL: BIOL (Biological study)
(cyclophilin C and A and B binding specificity for, of human)

RN 126374-37-6 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



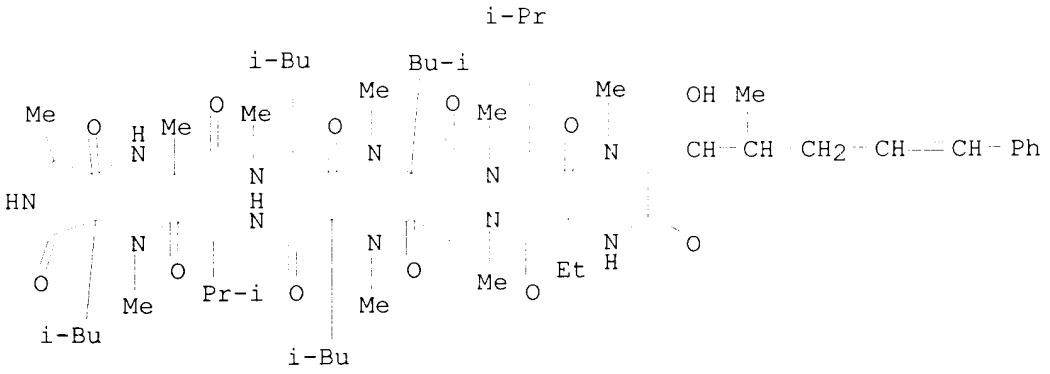
L15 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:179844 HCAPLUS
DOCUMENT NUMBER: 112:179844
TITLE: A semisynthetic approach to olefinic analogs of amino acid one (MeBMT) in cyclosporin A
AUTHOR(S): Park, Sang B.; Meier, G. Patrick

CORPORATE SOURCE: Dep. Med. Chem., Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Tetrahedron Letters (1989), 30(32), 4215-18
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:179844

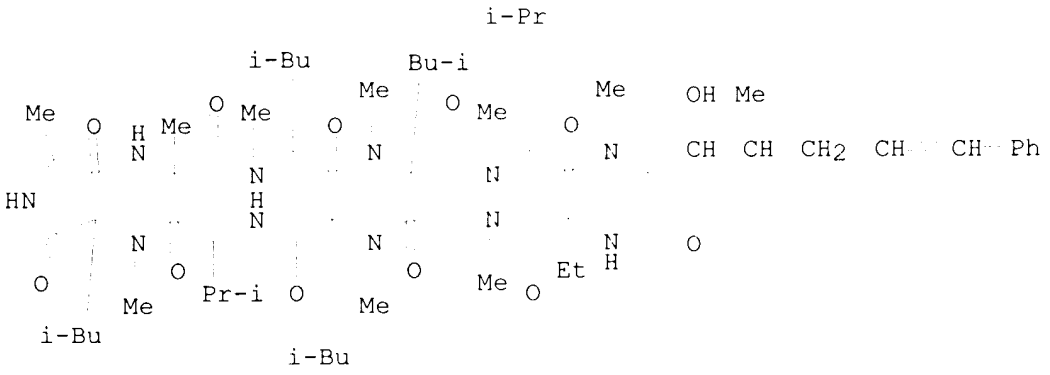
AB Four olefinic analogs of cyclosporin A at amino acid 1 (MeBMT), a residue crit. for the cyclophilin binding domain, were prepd. by a rapid, general, semisynthetic sequence involving oxidative degrdn. of the olefinic side chain followed by a Wittig olefination step.

IT **121700-70-7P 126374-37-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrogen and carbon-13 NMR of)

RN 121700-70-7 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R,6Z)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



RN 126374-37-6 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



L15 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:497723 HCAPLUS
DOCUMENT NUMBER: 111:97723

TITLE: Preparation, testing, and formulation of cyclosporins as drugs

INVENTOR(S): Bollinger, Pietro; Boelsterli, Johann Jakob; Borel, Jean Francois; Krieger, Manfred; Payne, Trevor Glyn; Traber, Rene P.; Wenger, Roland

PATENT ASSIGNEE(S): Sandoz A.-G., Switz.; Sandoz-Patent-G.m.b.H.; Sandoz-Erfindungen Verwaltungsgesellschaft m.b.H.

SOURCE: Eur. Pat. Appl., 40 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 296122	A2	19881221	EP 1988-810403	19880614
EP 296122	A3	19900620		
EP 296122	B1	19930929		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 95193	E	19931015	AT 1988-810403	19880614
ES 2059558	T3	19941116	ES 1988-810403	19880614
DK 8803265	A	19881218	DK 1988-3265	19880615
DK 173873	B1	20020121		
AU 8817679	A1	19881222	AU 1988-17679	19880615
AU 614086	B2	19910822		
CA 1338728	A1	19961119	CA 1988-569523	19880615
JP 01045396	A2	19890217	JP 1988-149227	19880616
JP 08032724	B4	19960329		
KR 9710927	B1	19970702	KR 1988-7330	19880616
ZA 8804345	A	19900228	ZA 1988-4345	19880617
US 5525590	A	19960611	US 1994-337346	19941110
JP 08048696	A2	19960220	JP 1995-208783	19950816
JP 2772372	B2	19980702		

PRIORITY APPLN. INFO.:

GB 1987-14090	A	19870617
GB 1987-14093	A	19870617
GB 1987-14098	A	19870617
GB 1987-14100	A	19870617
GB 1987-14115	A	19870617
GB 1987-14118	A	19870617
GB 1987-14119	A	19870617
GB 1987-14125	A	19870617
EP 1988-810403	A	19880614
US 1988-208422	B1	19880617
US 1991-704758	B1	19910523
US 1992-874676	B1	19920427
US 1993-67274	B1	19930524

OTHER SOURCE(S): MARPAT 111:97723

GI

A-B-X-MeLeu-Y-MeLeu-Ala-D-Ala-MeLeu-MeLeu-MeVal

I

A^1-B^1-X^1-MeLeu-Y^1-MeLeu-Ala-W-MeLeu-MeVal

II

A^2-B^2-Sar-MeLeu-Val-MeLeu-Ala-D-Ala-MeLeu-MeLeu-Z

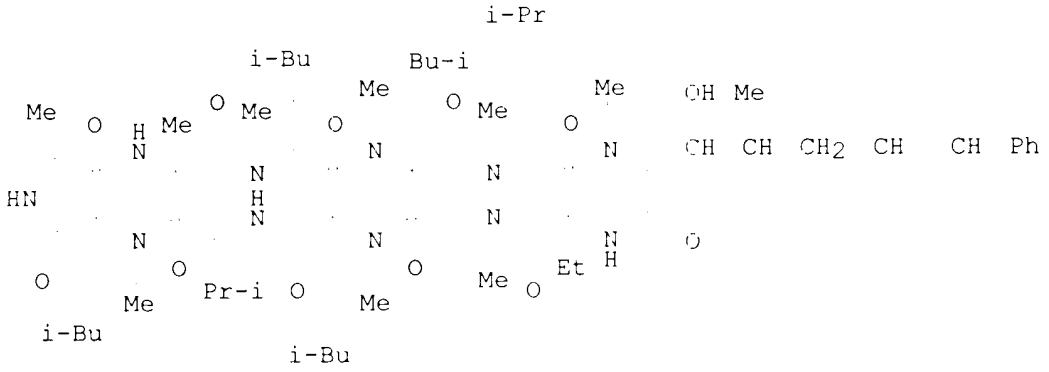
III

AB The title compds. (I, II, and III; A = 3'-O-acetyl-MeBmt; B = .alpha.Abu, Thr, Val, Nva; when B = .alpha.Abu, X = D-Ala, Y = Val; when B = Thr or Val, X = Sar, Y = Val; when B = Nva, X = Sar, Y = Val; or X = D-Ala, Y = Val; A1 = A, 3'-O-acyl-MeBmt; B1 = B, .beta.-O-acyl-.alpha.-amino acid residue; X1 = Sar, D-.alpha.-N-methylated .alpha.-amino acid residue; Y1 = Val, Nva; W = D-.beta.-hydroxy- or .beta.-O-acyl-.alpha.-amino acid residue; A2 = N-desmethyldihydro-MeBmt, B2 = Thr, Z = MeVal; or A2 = dihydro-MeBmt, B2 = Thr, Z = Val; or A = MeLeu, B = .alpha.-Abu, Z = Val; etc; MeBmt = N-methyl-4R-4-but-2E-en-1-yl-4-methyl-L-threonyl; .alpha.Abu = .alpha.-aminobutanoyl; Nva = norvalyl), useful as immunosuppressants, antiinflammatories, antiparasitics, and as adjuvants for coadministration against drug-resistant diseases, were prepd. Ciclosporin (III, A2 = MeBmt, B2 = .alpha.Abu, Z = MeVal) in THF was added to Li diisopropylamide in THF at -78.degree. and after 1/2 h MeOCOCl was added. Stirring was continued for 1 h at -78.degree. to give III (A2 = 3'-O-methoxycarbonyl-MeBmt, B2 = .alpha.Abu, Z = MeVal). I, II, and III at 1-20 mg/day orally in cancer patients with multiple drug-resistant tumors restricted tumor growth and decreased metastases.

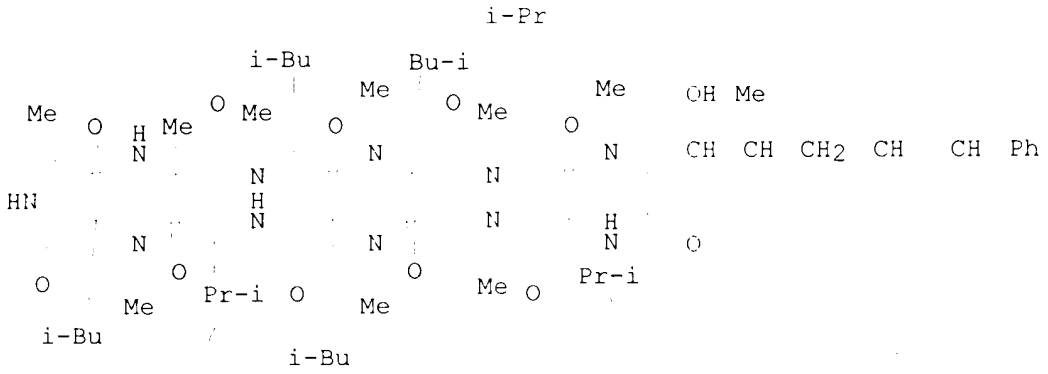
IT **111722-68-0P 121584-39-2P 121584-43-8P**
121584-50-7P 121700-70-7P 121700-71-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as drug adjuvant, immunosuppressant, antiinflammatory, and parasiticide)

RN 111722-68-0 HCAPLUS

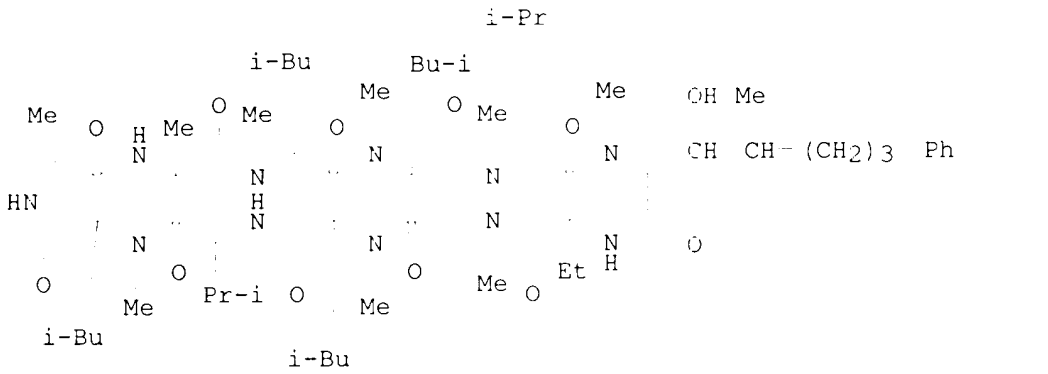
CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



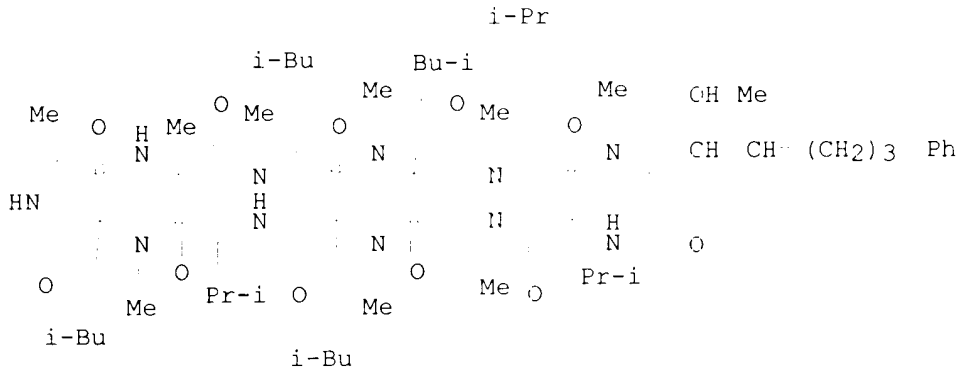
RN 121584-39-2 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R,6Z)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]-7-L-valine- (9CI) (CA INDEX NAME)



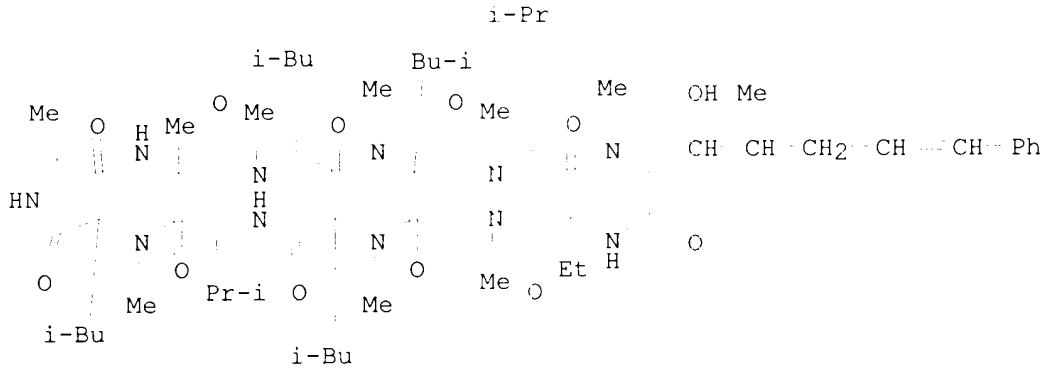
RN 121584-43-8 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



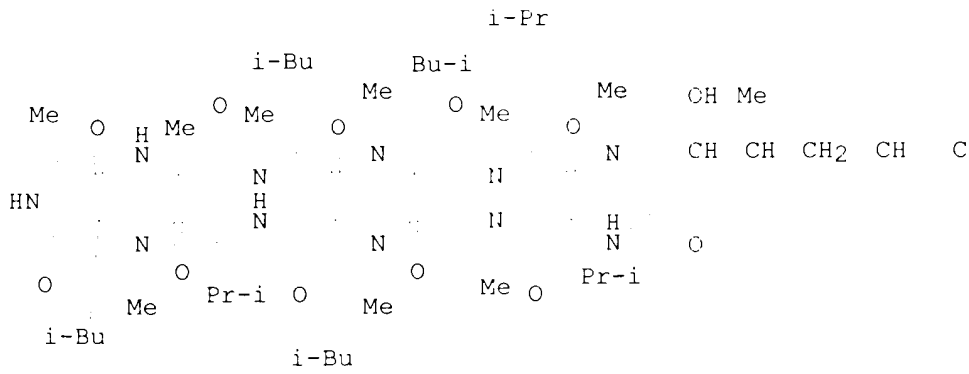
RN 121584-50-7 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]-7-L-valine- (9CI) (CA INDEX NAME)



RN 121700-70-7 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R,6Z)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



RN 121700-71-8 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]-7-L-valine- (9CI) (CA INDEX NAME)

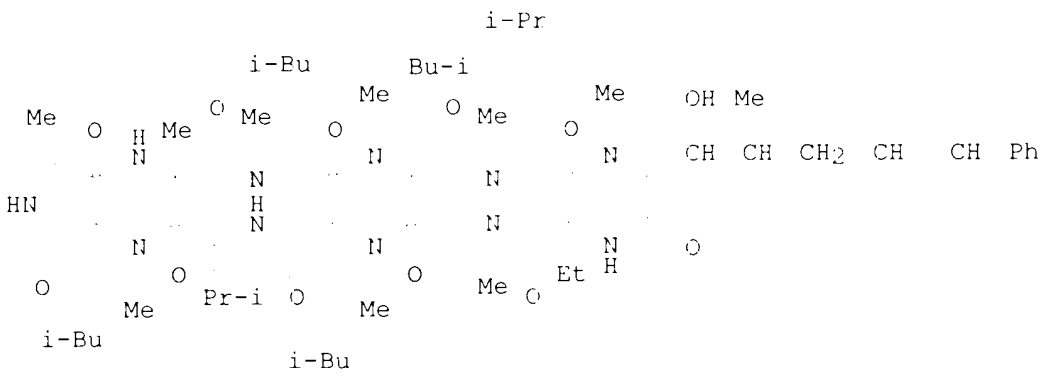


L15 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1988:416575 HCAPLUS
DOCUMENT NUMBER: 109:16575
TITLE: Study of the conformation of cyclosporine in aqueous medium by means of monoclonal antibodies
AUTHOR(S): Quesniaux, Valerie F. J.; Wenger, Roland M.; Schmitter, Doris; Van Regenmortel, Marc H. V.
CORPORATE SOURCE: Lab. Immunochem., Inst. Mol. Cell. Biol., Strasbourg, 67084, Fr.
SOURCE: International Journal of Peptide & Protein Research (1988), 31(2), 173-85
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The three-dimensional structure of the immunosuppressive cyclic peptide cyclosporine (Cs), detd. in crystal by X-ray anal. and in soln. in aprotic solvents by NMR, differs mainly by the orientation of the 7 carbon side chain of residue 1. Because of its poor soly. in water, the conformation of Cs in aq. medium cannot be studied by NMR methods, which require concns. of the substance of the order of milligram/mL, but can be analyzed by immunochem. methods in which concns. in the nanogram/mL range are detected. In the present study, the ability of a series of monoclonal antibodies (McAbs) raised against Cs to recognize different parts of residue 1 of Cs was detd. from the cross-reactivity of different Cs-analogs modified in residue 1. When Cs is dissolved in aq. buffer, the terminal atoms of residue 1 side chain are not available for binding to antibodies recognizing the face of the mol. defined by residues 1, 2, 3, 10, 11, suggesting that the chain is probably folded back under the mol., as obsd. in the crystal structure. Binding of McAbs to Cs was also affected by conformational modifications of the peptide ring that occur in some Cs-analogs. The results illustrate the potential of McAbs for probing the conformation of Cs-derivs. for which no structural data are available.

IT **111722-68-0**
RL: PRP (Properties)
(conformation of, monoclonal antibodies recognition of)
RN 111722-68-0 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)

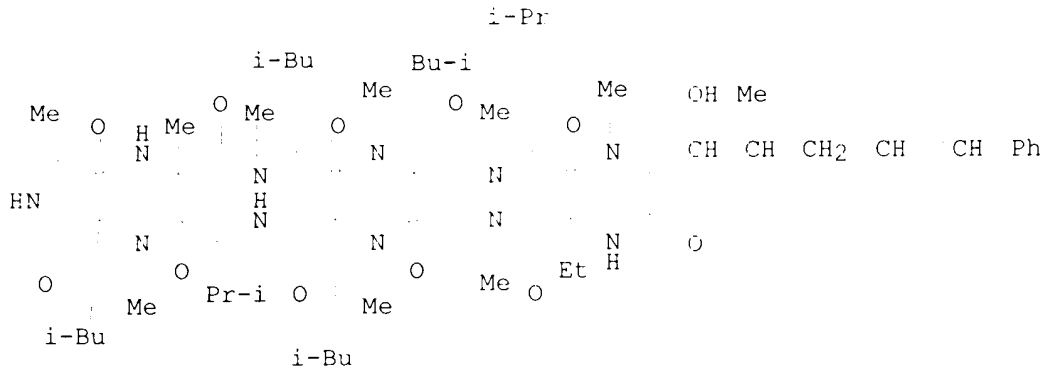


L15 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1988:143029 HCAPLUS
DOCUMENT NUMBER: 108:143029
TITLE: Cyclophilin binds to the region of cyclosporine involved in its immunosuppressive activity
AUTHOR(S): Quesniaux, Valerie F. J.; Schreier, Max H.; Wenger, Roland M.; Hiestand, Peter C.; Harding, Matthew W.; Van Regenmortel, Marc H. V.
CORPORATE SOURCE: Lab. Immunochim., Inst. de Biol. Mol. Cell., Strasbourg, F-67084, Fr.
SOURCE: European Journal of Immunology (1987), 17(9), 1359-65
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, a quant. immunoassay for cyclophilin was developed which made it possible to compare its relative affinity for cyclosporine and any of its analogs. The binding of cyclophilin to cyclosporine coated on a solid phase was revealed by anticyclophilin rabbit antiserum followed by antiglobulin-enzyme conjugate. This reaction was inhibited by addn. of free cyclosporine or certain cyclosporine analogs. By studying the binding of cyclophilin to more than 50 cyclosporine derivs. modified singly on each of the 11 amino acid residues, it was shown that cyclophilin binds to the residues of cyclosporine known to be crit. for its immunosuppressive activity. Thus, cyclophilin as a highly discriminating stereospecific binding protein for cyclosporine.

IT **111722-68-0**
RL: BIOL (Biological study)
(cyclophilin binding to, specificity of, immunosuppression in relation to)
RN 111722-68-0 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)

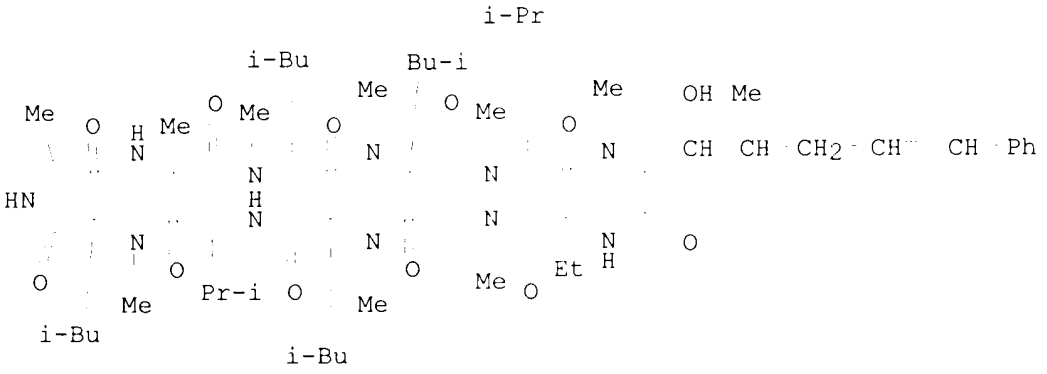


L15 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:36050 HCAPLUS
DOCUMENT NUMBER: 108:36050
TITLE: Fine specificity and cross-reactivity of monoclonal antibodies to cyclosporine
AUTHOR(S): Quesniaux, Valerie F. J.; Tees, Reet; Schreier, Max H.; Wenger, Roland M.; Van Regenmortel, Marc

H. V.
CORPORATE SOURCE: Sandoz Ltd., Basel, CH-4002, Switz.
SOURCE: Molecular Immunology (1987), 24(11), 1159-68
CODEN: MOIMD5; ISSN: 0161-5890
DOCUMENT TYPE: Journal
LANGUAGE: English
AB More than 180 monoclonal antibodies (McAbs) to the cyclic undecapeptide cyclosporine (Cs) have been prepd. Several immunization protocols and antibody screening processes were compared. Two main groups of McAbs recognizing different sides of the Cs mol. could be differentiated. The antibodies belonged to the IgG and IgA classes and showed high affinity for Cs. Based on their ability to discriminate Cs-derivs. modified singly at each of the 11 residues of the Cs mol., the antigenic recognition pattern of different McAbs was studied at the level of individual residues. Closely related recognition patterns were found in each of the 2 main McAb groups. The apparent size of the Cs antigenic sites recognized by different McAbs varied from 4-10 residues and did not correlate with antibody affinity.

IT **111722-68-0**
RL: BIOL (Biological study)
(cyclosporine-specific monoclonal antibodies cross-reactivity with)

RN 111722-68-0 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI) (CA INDEX NAME)



FILE 'CAOLD' ENTERED AT 15:32:29 ON 07 JAN 2003
L16 0 S L14

FILE 'USPATFULL' ENTERED AT 15:32:36 ON 07 JAN 2003
L17 1 S L14

L17 ANSWER 1 OF 1 USPATFULL
ACCESSION NUMBER: 96:50887 USPATFULL
TITLE: Cyclosporins and their use as pharmaceuticals
INVENTOR(S): Bollinger, Pietro, Bottmingen, Switzerland
Bolsterli, Johann J., Buus, Switzerland
Payne, Trevor G., Bern; all of, Switzerland
PATENT ASSIGNEE(S): Sandoz Ltd., Basel, Switzerland (non-U.S. corporation)

Searcher : Shears 308-4994

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5525590		19960611
APPLICATION INFO.:	US 1994-337346		19941110 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-67274, filed on 24 May 1993, now abandoned which is a continuation of Ser. No. US 1992-874676, filed on 27 Apr 1992, now abandoned which is a continuation of Ser. No. US 1991-704758, filed on 23 May 1991, now abandoned which is a continuation of Ser. No. US 1988-208422, filed on 17 Jun 1988, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1987-14090	19870617
	GB 1987-14093	19870617
	GB 1987-14098	19870617
	GB 1987-14100	19870617
	GB 1987-14115	19870617
	GB 1987-14118	19870617
	GB 1987-14119	19870617
	GB 1987-14125	19870617

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Russel, Jeffrey E.
LEGAL REPRESENTATIVE: Honor, Robert S., Kassenoff, Melvyn M., McGovern, Thomas O.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 2011
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Cyclosporins wherein the residue at the 1-position (typically -MeBmt- or -dihydro-MeBmt-) is 3'O-acylated or 3'-oxo or -C.sub.1-4 alkoxyimino substituted, or wherein the residue at the 2-position is .beta.-O-acyl or .beta.-oxo substituted, or wherein the residue at the 2-position is -Ile-, or wherein the residue at the 11-position is -MeAls-, -MeIle- or -MealloIle- as well as various naturally occurring cyclosporins/dihydro-derivatives thereof, are useful in reversing resistance to chemotherapy, in particular resistance to cytostatic or anti-neoplastic therapy. Various of these cyclosporins and intermediates for their production are novel. Intermediates wherein the residue (e.g. -MeBmt-, -dihydro-MeBmt- etc.) at the 1-position is 8'-alkoxy or 7'-desmethyl-7'-hydrocarbyl substituted are novel and useful as immunosuppressants, anti-inflammatory and anti-parasitic agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> fil hom
FILE 'HOME' ENTERED AT 16:04:28 ON 07 JAN 2003

Seq.

FILE 'REGISTRY' ENTERED AT 11:05:24 ON 08 JAN 2003
ACT LIUS1/A

L1 (1039) SEA FILE=REGISTRY ABB=ON PLU=ON LVLA.LLV/SQSP
L2 890 SEA FILE=REGISTRY ABB=ON PLU=ON L1 AND CYCL?/NTE ← requires that seq. is cyclic

FILE 'HCAPLUS' ENTERED AT 11:05:57 ON 08 JAN 2003
L1 (1039) SEA FILE=REGISTRY ABB=ON PLU=ON LVLA.LLV/SQSP
L2 890 SEA FILE=REGISTRY ABB=ON PLU=ON L1 AND CYCL?/NTE
L8 393 SEA FILE=HCAPLUS ABB=ON PLU=ON L2(L)ADMIN?
L9 186 SEA FILE=HCAPLUS ABB=ON PLU=ON L8(L)(TREAT? OR THERAP? OR PREVENT?)
L10 39 SEA FILE=HCAPLUS ABB=ON PLU=ON L9(L)((?TRANSPLANT? OR ?GRAFT?)(5A)REJECT? OR (AUTOIMMUN? OR AUTO IMMUN?)(5A)(DISEAS? OR DISORDER) OR (CONICAL OR EPITHEL?)(W)CORNEA# OR KERATIT? OR LEU!OMA OR MOOREN?(1W)ULCER OR SCLEVIT? OR GRAVE?(1W)OPHTHALMOPATH?)

L10 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:534045 HCAPLUS
DOCUMENT NUMBER: 131:165308
TITLE: Use of fructose diphosphate to decrease the amount of cyclosporin administration after organ transplantation
INVENTOR(S): Markov, Angel K.
PATENT ASSIGNEE(S): Cypros Pharmaceutical Corp, USA
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11228442	A2	19990824	JP 1998-27047	19980209

PRIORITY APPLN. INFO.: JP 1998-27047 19980209

AB Allograft rejection by organ transplant recipients is suppressed by administration of (a) cyclosporins at the amts. pharmacol. acceptable for suppression of the T-lymphocyte activation responses after organ transplantation and (b) fructose 1,6-diphosphate (FDP) at the amts. pharmacol. acceptable for decrease of the amts. of the cyclosporins. FDP showed approx. the same inhibitory activity as cyclosporin A against thymidine intake by conA-stimulated T-lymphocytes but did not affect the cell viability.

IT **59865-13-3**, Cyclosporin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fructose diphosphate **administration** to decrease the amt. of cyclosporin for **prevention** of **allograft rejection** after organ **transplantation**)

L10 ANSWER 2 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:188649 HCAPLUS
DOCUMENT NUMBER: 106:188649

TITLE: Transplantation of the entire small bowel in inbred rats using cyclosporine
AUTHOR(S): Hatcher, Paul A.; Deaton, David H.; Bollinger, R. Randal
CORPORATE SOURCE: Med. Cent., Duke Univ., Durham, NC, 27710, USA
SOURCE: Transplantation (1987), 43(4), 478-84
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inbred strains of rats were used to analyze unidirectional host-vs.-**graft** disease (**transplant rejection**) without **graft**-vs.-host disease in small intestinal transplants and the immunosuppressive properties of cyclosporine (CsA) [**59865-13-3**]. Forty-six Lewis rats received heterotopic transplants of the entire small bowel in 4 groups: (1) Lewis-to-Lewis isografts, without CsA; (2) Lewis-to-Lewis isografts, with CsA (15 mg/kg/day); (3) (Lewis .times. ACI)F1-to Lewis allografts, without CsA; (4) (Lewis .times. ACI)F1-to Lewis allografts, with CsA. Small bowel rejection was assocd. with gross morphol. changes that preceded all other findings. A histol. scoring system assessed the degree of **transplant rejection**. A characteristic transient wt. loss was seen in animals rejecting their bowels. Glucose absorption was impaired and polyethylene glycol absorption increased during rejection. Cyclosporine inhibited all of these changes in allografted rats. It is concluded that daily **administration** of cyclosporine is effective in **preventing** the morphol. and functional changes of acute **transplant rejection** in intestinal **allografts** and does not change these parameters in **transplants** that are not **rejecting**.

L10 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:27550 HCAPLUS
DOCUMENT NUMBER: 106:27550
TITLE: Neuroanatomical evidence of reinnervation in primate allografted (transplanted) skin during cyclosporine immunosuppression
AUTHOR(S): Samulack, Donald D.; Munger, Bryce L.; Dykes, Robert W.; Daniel, Rollin K.
CORPORATE SOURCE: R. Victoria Hosp., McGill Univ., Montreal, QC, H3A 1A1, Can.
SOURCE: Neuroscience Letters (1986), 72(1), 1-6
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two primate upper-extremity composite tissue allograft models were studied using the baboon; (1) unidirectional allograft of the complete soft tissue coverage of the index finger, and (2) unidirectional allograft of a single whole hand. **Therapeutic** levels of cyclosporine [**59865-13-3**] were **administered** rendering the animals selectively immunosuppressed with respect to cytotoxic T-cell activity, thereby minimizing **allograft rejection**. The animals were euthanized 5-10 mo postoperatively and the allografts were removed and evaluated histol. Evidence is presented documenting the reinnervation of sensory mechanoreceptors across major histocompatibility barriers in allografted baboon skin. Meissner and pacinian corpuscles as well as hair follicles, showed a spectrum

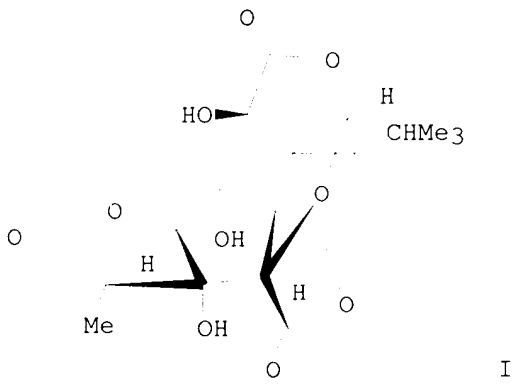
of reinnervation by host axons.

L10 ANSWER 4 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:367 HCAPLUS
DOCUMENT NUMBER: 106:367
TITLE: Circadian stage-dependent prolongation by cyclosporine of segmental pancreatic allograft function in the rat
AUTHOR(S): Cavallini, M.; Halberg, F.; Tao, L.; Sutherland, D. E. R.
CORPORATE SOURCE: Policlin. Umberto I, Univ. Rome, Rome, I-00161, Italy
SOURCE: European Surgical Research (1986), 18(6), 375-82
CODEN: EUSRBM; ISSN: 0014-312X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Direct **therapeutic** benefit from the improvement of the desired effect was obtained by the circadian timing of i.p. cyclosporine (Cs) [**59865-13-3**] **administration** to Lewis rats bearing an ACI segmental pancreas allograft. Under conditions of light (L) and darkness (D) alternating at 12-h intervals, staggered by 8 h in 3 rooms kept at 24.degree., the effect of Cs in delaying **graft rejection** was improved by timing. When the mean time to rejection during the L span is equated to 100%, graft function is prolonged by 40% at the right time (injection daily during the D span) as compared to the wrong time (injection daily during the L span).

L10 ANSWER 5 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:618590 HCAPLUS
DOCUMENT NUMBER: 105:218590
TITLE: Concanavalin A-dependent cell-mediated cytotoxicity in bronchoalveolar lavage fluid. Correlation with lung allograft rejection in mongrel dogs during cyclosporine dose tapering
AUTHOR(S): Norin, Allen J.; Kamholz, Stephan L.; Pinsker, Kenneth L.; Emeson, Eugene E.; Veith, Frank J.
CORPORATE SOURCE: Montefiore Med. Cent., Albert Einstein Coll. Med., Bronx, NY, 10467, USA
SOURCE: Transplantation (1986), 42(5), 466-72
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A concanavalin A (con A)-dependent cell-mediated cytotoxicity (CDCMC) assay was used to examine the development of intragraft and peripheral blood cytolytic T-lymphocyte activity during cyclosporine (CsA) [**59865-13-3**] dose tapering. These studies were conducted in a canine single-lung transplantation model that facilitates serial examn. of intragraft effector cells by bronchoalveolar lavage (BAL). A remarkable correlation of increased intragraft CDCMC and clin. evidence of lung **allograft rejection** was obsd. during CsA dose tapering in some recipients. In other recipients CDCMC remained low and evidence of rejection was not obsd. during drug tapering. In contrast, peripheral blood CDCMC did not correlate well with evidence of rejection. Rejection phenomena obsd. after termination of CsA **therapy** were reversed by resumption of CsA **treatment** but were not reversed by **administration** of

methylprednisolone. Furthermore, the increased level of CDCMC was diminished by reinstitution of CsA **therapy** at the initial dosage. Following termination of CsA **therapy**, a prolonged period of unresponsiveness was obsd. in nearly two-thirds of the recipients, and 60% of these latter dogs had unlimited survival of their lung allografts (median >496 days). Intragraft CDCMC remained low during the periods of unresponsiveness and increased upon onset of rejection. Thus, measurement of intragraft CDCMC is a useful in vitro method of monitoring lung **allograft rejection**, and therefore provides a technique for adjusting CsA dosage schedules to achieve maximally effective immunosuppression. The use of this assay for monitoring **rejection** of other organ **grafts** requires further investigation.

L10 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:546176 HCAPLUS
DOCUMENT NUMBER: 105:146176
TITLE: Prolongation of cardiac allograft survival with BN 52021, a specific antagonist of platelet-activating factor
AUTHOR(S): Foegh, Marie L.; Khirabadi, Bijan S.; Rowles, John R.; Braquet, Pierre; Ramwell, Peter W.
CORPORATE SOURCE: Med. Cent., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Transplantation (1986), 42(1), 86-8
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB **Treatment** of rat cardiac allograft recipients with BN 52021 (I) [99796-69-7] in combination with azathioprine (Aza) [446-86-6] or cyclosporin A (CsA) [**59865-13-3**] delayed **graft rejection**. The doses of Aza and CsA by themselves did not prolong graft survival. The combination of I + Aza was more effective in prolonging graft survival than the traditional immunosuppressive combination of Aza + prednisolone

[50-24-8]. The improved prolongation of cardiac graft survival in recipients **treated** with I combined with Aza or CsA, when compared with Aza and CsA **administered** by themselves, suggested a causal role for platelet-activating factor [65154-06-5] in promoting cardiac **allograft rejection**.

L10 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:218795 HCAPLUS
DOCUMENT NUMBER: 104:218795
TITLE: Effect of cyclosporin A on mercury-induced autoimmune glomerulonephritis in the Brown Norway rat
AUTHOR(S): Baran, D.; Vendeville, B.; Vial, M. C.; Cosson, C.; Bascou, C.; Teychenne, P.; Druet, P.
CORPORATE SOURCE: Hop. Broussais, Paris, 75674, Fr.
SOURCE: Clinical Nephrology (1986), 25(Suppl. 1), S175-S180
CODEN: CLNHBI; ISSN: 0301-0430
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rats with HgCl2-induced nephritis were **treated** with varying doses of cyclosporin A (I) [**59865-13-3**] for 2 mo. All manifestations of HgCl2-induced disease were **prevented** in rats **treated** concurrently with I at 7 or 10 mg/kg/day. Partial suppression was evident at lower daily doses, but not with bi-weekly I **administration**. The initial phase of HgCl2-induced nephritis could be completely suppressed with a 15-day course of I. The later phase of the disease could be temperated by I **administration** starting on day 10 after the 1st HgCl2 injection. The optimal regimen of 7 mg/kg/day for 60 days was not assocd. with any evidence of I toxicity. I appears to interfere with the polyclonal activation of B cells obsd. in HgCl2-induced **autoimmune disease**, accounting for its striking **preventive** and curative effect in this model.

L10 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:81697 HCAPLUS
DOCUMENT NUMBER: 104:81697
TITLE: Paradoxical augmentation of tuberculin-like hypersensitivity, but not Jones-Mote or contact hypersensitivity, in cyclosporin A treated guinea pigs
AUTHOR(S): Aldridge, R. D.; Thomson, A. W.
CORPORATE SOURCE: Dep. Pathol., Univ. Aberdeen, UK
SOURCE: International Archives of Allergy and Applied Immunology (1986), 79(3), 225-30
CODEN: IAAAAM; ISSN: 0020-5915
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Administration** of cyclosporin A (CsA) [**59865-13-3**] (25 mg/kg) orally to guinea pigs from the time of immunization with ovalbumin (OVA) in complete Freund's adjuvant, followed by drug withdrawal 4 days later, resulted in marked potentiation of classical, tuberculin-like delayed-hypersensitivity skin responses to OVA. However, no such augmentation of delayed-type hypersensitivity (DTH) to purified protein deriv. (PPD) was demonstrated. The enhancing effect of CsA was also dependent on the dose of OVA used for both immunization and skin testing and on the

interval between drug withdrawal and the elicitation of DTH. A single i.p. injection of CsA (200 mg/kg) given 2 days before immunization also enhanced the 14-day responses to OVA. Similar **treatment** protocols, however, did not enhance Jones-Mote (cutaneous basophil) hypersensitivity to OVA or contact sensitivity reactions to dinitrofluorobenzene. Longer courses of CsA (25 mg/kg) between sensitization and skin testing severely depressed all 3 categories of type IV hypersensitivity reactions. These observations may have important cautionary implications for the prospective management of immunol. mediated **diseases** of intermittent activity, including certain **autoimmune disorders**, where short courses of CsA might be contemplated.

L10 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:45466 HCAPLUS
DOCUMENT NUMBER: 104:45466
TITLE: Cyclosporine and experimental skin allografts. II. Indefinite survival and development of specific immunologic unresponsiveness
AUTHOR(S): Towpik, Edward; Kupiec-Weglinski, Jerzy W.; Schneider, Tobin M.; Tyler, Douglas; Padberg, Winfried; Araneda, Dorian; Tilney, Nicholas L.
CORPORATE SOURCE: Surg. Res. Lab., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Transplantation (1985), 40(6), 714-18
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunol. unresponsivenes toward skin allografts was studied in cyclosporine (CsA) [**59865-13-3**]-**treated** rats. BN skin grafts survive about 22 days and about 34 days in LEW hosts following 7 or 14 days of daily CsA **treatment** (15 mg/kg/day), resp.; in unmodified hosts **grafts** are **rejected** by 9 days. Indefinite (>100 days) survival can, however, be produced by **administering** maintenance 15 mg/kg CsA every 4th day, following an initial course of the agent for 14 days. Early signs of **graft rejection** (hair loss, localized epidermal breakdown, and ulcerations) occurring in some animals were reversed by a CsA pulse (15 mg/kg/day) for 7 days, reduced gradually to the maintenance dose. CsA was equally effective when started as late as 4 days after grafting, but ineffective when started after day 4. Once BN **grafts** were **rejected**, the agent could not **prevent** 2nd-set **rejection** of donor-specific **grafts**, but significantly prolonged the survival of 3rd-party (WF) skins. Survival of original BN grafts was unchanged by the placement of 2nd BN grafts during both the inductive and maintenance phases; these 2nd grafts survived as long as the original grafts. In contrast, secondary 3rd-party (WF) **grafts** were promptly **rejected**; their destruction did not influence survival of the original grafts. Thus, indefinite survival of rat skin allografts is feasible with low maintenance doses of CsA. **Graft rejection** at later stages can be reversed by resuming daily **therapy**. Host unresponsiveness is stable and specific both during the early inductive and later maintenance phases. These observations are pertinent to **treatment** of skin allografts after burns or in skin defects.

L10 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:28330 HCAPLUS
DOCUMENT NUMBER: 104:28330
TITLE: Effect of renal allograft dysfunction upon cyclosporine trough levels in host blood
AUTHOR(S): Arnold, Angelo N.; Waltzer, Wayne C.; Anaise, David; Weinstein, Stephen W.; Rapaport, Felix T.
CORPORATE SOURCE: Health Sci. Cent., State Univ. New York, Stony Brook, NY, 11794-8192, USA
SOURCE: Transplantation (1985), 40(6), 605-10
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics of cyclosporine (CsA) [**59865-13-3**] in humans with dysfunction of the transplanted kidney were studied. Decreases in CsA dosage in such patients failed to result in a significant lowering in trough levels. **Therapeutic** CsA trough levels were generally at the 70-140 ng/mL level; at the time of rejection, the same doses of CsA resulted in a rise of trough levels to 300-500 ng/mL. As the rejection crises resolved and kidney function improved, the CsA serum trough levels returned to their lower levels. These results suggest that the urinary elimination of CsA and its metabolites may be a key determinant of CsA trough levels, and that the status of renal function at the time of testing must be considered in the interpretation of the data. In support of this observation, the CsA concns. in 4-6 h post-CsA-**administration** urine samples ranged from 400 ng/mL to 4500 ng/mL, as measured by HPLC. The data suggest that rising CsA trough levels in a previously stable recipient may serve as a valuable early warning index of impending **allograft** dysfunction (**rejection**, infection, and obstruction). This appears particularly true during the 1st 30 days after renal **transplantation**, when the incidence of **rejection** is the greatest in this patient population.

L10 ANSWER 11 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:553619 HCAPLUS
DOCUMENT NUMBER: 103:153619
TITLE: Effects of systemic administration of Chlorambucil and topical application of Cyclosporin A on corneal graft survival in rabbits
AUTHOR(S): Levinger, S.; Zauberman, H.
CORPORATE SOURCE: Dep. Ophthalmol., Hadassah Univ. Hosp., Jerusalem, 91120, Israel
SOURCE: Israel Journal of Medical Sciences (1985), 21(8), 670-4
CODEN: IJMDAI; ISSN: 0021-2180
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of topically **administered** Cyclosporin A [**59865-13-3**] and of systemically **administered** Chlorambucil [305-03-3] (2 mg/kg per day) were studied for 6 wk in 32 rabbits that underwent penetrating corneal graft in 1 eye, followed 2 wk later by a skin graft from the donor animal. Nine rabbits were topically **treated** with 1% Cyclosporin A soln. 5 times daily for 6 wk. Of these, 3 eyes showed no rejection; 4 eyes Grade 1-2 rejection; and 1 eye Grade 3 rejection. No animal

showed total rejection (Grade 4). Thus, both compds. have a beneficial effect on corneal **grafts** challenged by a second-set **rejection**.

L10 ANSWER 12 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:214781 HCAPLUS
DOCUMENT NUMBER: 102:214781
TITLE: Immunostimulatory properties of ethylene-2,2'-bis(dithio)bis(ethanol) and related compounds in vivo
AUTHOR(S): Hiestand, P. C.; Strasser, M.
CORPORATE SOURCE: Preclin. Res., Sandoz Ltd., Basel, CH-4002, Switz.
SOURCE: International Journal of Immunopharmacology (1985), 7(1), 141-51
CODEN: IJIMDS; ISSN: 0192-0561
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title compd. ADA 202-718 [83791-86-0], as well as 2-hydroxyethyl disulfide (HEDS) [1892-29-1] and higher homologs of ADA 202-718, were found to profoundly stimulate the delayed type hypersensitivity reaction in mice when given i.p. or orally in a dose range of 0.1-10 mg/kg. While even a single application of ADA 202-718 at the time of sensitization resulted in a stimulation of the hypersensitivity reaction, **administration** of the compd. at the time of challenge was without effect. When ADA 202-718 was given to animals which were subjected to immunosuppressive **therapy** by cyclosporine [**59865-13-3**], the suppressed hypersensitivity reaction was restored to normal. At much higher doses (50-200 mg/kg) ADA 202-718 enhanced the local graft-vs-host reaction in the rat. ADA 202-718 did not interfere with the suppressed graft-vs-host reaction obtained by immunosuppressive **treatment** with cyclosporine nor with the immunosuppressed skin **transplant rejection**. Single applications of HEDS or ADA 202-718 enhanced the humoral response of mice to sheep erythrocytes as well as to haptenized sheep or chicken erythrocytes. Although antibody levels at the time of maximal antibody prodn. (day 4 for IgM) were only moderately enhanced, elevated antibody titers (IgM and IgG) were found even 23 days after sensitization. The age-dependent decreased humoral response of mice to sheep erythrocytes tended to be partially restored by twice weekly oral applications of HEDS or ADA 202-718 (0.1 to 1 mg/kg for 4 wk). ADA 202-718 did not decrease the swelling in the Freund's adjuvant induced arthritis in the rat, but reduced the pain in this model. Swelling in a locally induced edema was reduced in a dose-dependent fashion. ADA 202-718 was more effective than acetylsalicylic acid in alleviating the edema-assocd. pain.

L10 ANSWER 13 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:197677 HCAPLUS
DOCUMENT NUMBER: 102:197677
TITLE: Reversal of cyclosporine-induced mortality with a synthetic polymeric immunostimulant in a murine model of fecal peritonitis
AUTHOR(S): Moffat, Frederick L.; Falk, Rudolf E.; Teodorczyk-Injeyan, Julita; Clark, A. Gavin; Gilas, Tomas; Falk, Michael; Dalfen, Richard;

Rotstein, Lorne E.; McDonell, Michele; et al.
CORPORATE SOURCE: Dep. Surg., Univ. Toronto, Toronto, ON, M5G 1L7, Can.
SOURCE: Transplantation (1985), 39(4), 369-74
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Copovithane (Cpv) [68045-74-9] prolonged survival of the animals in a murine cecal ligation, puncture, and excision (CLPE) model; the optimal dose for this effect was 100 mg/kg. Cyclosporine (CsA) [**59865-13-3**] had a significant and deleterious effect on the survival of the animals at several dosage levels when **administrated** 48 and 24 h before cecal ligation, and immediately before and 16 h after cecal ligation. Mice **treated** with CsA (in a dose sufficient to **prevent** skin **allograft rejection**) plus Cpv had a longer survival time than mice **treated** with CsA alone; furthermore, the survival of CsA-plus-Cpv-**treated** animals was not significantly different from that of saline-**treated** controls. Acceptance and survival of H-2 incompatible skin allografts in mice **treated** with CsA were not affected by Cpv 100 mg/kg/wk. Thus, CsA-induced mortality in the CLPE model can be abrogated by Cpv without adversely affecting skin allograft survival.

L10 ANSWER 14 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:160165 HCAPLUS
DOCUMENT NUMBER: 102:160165
TITLE: The effect of cyclosporine on the nature and extent of lymphocyte infiltration in rat cardiac allografts
AUTHOR(S): Chisholm, P. M.; Cox, J. H.; Yacoub, M. H.
CORPORATE SOURCE: Chelsea Coll., Univ. London, Middlesex, UK
SOURCE: Transplantation Proceedings (1985), 17(1, Book 2), 1357-61
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rats, lymphocyte subpopulations (helper and suppressor/cytotoxic cells) were increased in cyclosporine (I) [**59865-13-3**]-**treated**, but not in untreated, cardiac graft recipients. In recipients of both allogenic and syngeneic grafts, the proportions of these cells increased progressively from the time of **administration** of I and returned to normal when the drug was discontinued. The only changes that were exclusive to the untreated recipients of allogeneic **grafts** and that preceded **graft rejection** were a progressive fall in the proportion of helper T cells and a rise in the proportion of Ia-pos. cells. There was a preponderance of T cells of the suppressor/cytotoxic cell phenotype in **rejecting grafts** at the time of maximal infiltration but not in the grafts of I-**treated** recipients. A substantial majority of the leukocytes in **rejecting allografts**, immediately preceding **rejection**, were Ia-pos.

L10 ANSWER 15 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:142891 HCAPLUS
DOCUMENT NUMBER: 102:142891

TITLE: Cyclosporine in concordant renal hare-to-rabbit xenotransplantation: prolongation and modification of rejection, and adverse effects
AUTHOR(S): Kemp, E.; Starklint, H.; Larsen, S.; Dieperink, H.
CORPORATE SOURCE: Dep. Nephrol., Odense Univ. Hosp., Odense, DK-5000, Den.
SOURCE: Transplantation Proceedings (1985), 17(1, Book 2), 1351-6
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB At 10 mg/kg/day (i.m.) and at 15 mg/kg/day (orally or i.m.), cyclosporine (I) [**59865-13-3**] modified or delayed the concordant (hare-to-rabbit) **xenograft rejection**. I (20 mg/kg/day, i.m.) had an undesirable effect on renal function and structure resulting in glomerular microthrombosis. Signs of toxicity (gingival hyperplasia and muscular atrophy) were seen with 60 mg I/kg, i.m. (twice weekly) doses. High doses of I (including i.v. **administration**) resulted in graft failure and biopsy alterations were similar to those of hyperacute rejection. Rabbits do not tolerate long-term **treatment** with I in doses that are well tolerated by other species including humans.

L10 ANSWER 16 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:125249 HCAPLUS
DOCUMENT NUMBER: 102:125249
TITLE: Induction of donor-specific unresponsiveness in rat kidney transplantation with donor antigen and three cycles of cyclosporine
AUTHOR(S): Kahan, B. D.; Yoshimura, N.; Yasumura, T.
CORPORATE SOURCE: Med. Sch., Univ. Texas, Houston, TX, USA
SOURCE: Transplantation Proceedings (1985), 17(1, Book 2), 1387-90
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In Wistar-Furth rats receiving kidney transplants from Buffalo rats, **treatment** with donor antigen from Buffalo spleen cells on the day before the operation and with cyclosporine [**59865-13-3**] (10 mg/kg,/day, orally, on the day before, of, and after the operation and 2 more 3-dose cycles at 5- or 7-day intervals afterwards) prolonged graft survival. **Administration** of 3 cycles of cyclosporin alone at 10-day intervals after the operation did not prolong the graft survival. However, 3 cyclosporine cycles at 10-day intervals combined with a single dose of antigen prolonged survival. Thus, if early sensitization is averted by the antigen-cyclosporine regimen, multiple cyclosporine dose cycles may induce long-term depression of helper T cells. In rats in which prolonged transplant survival was induced, a skin transplant from a Buffalo rat was not **rejected**, but a 3rd party **graft** from a brown Norway rat was rejected.

L10 ANSWER 17 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:125236 HCAPLUS
DOCUMENT NUMBER: 102:125236
TITLE: Mechanism of allograft rejection: mode of

action of cyclosporine and passive enhancement
AUTHOR(S): Bradley, J. A.; Mason, D. W.; Morris, P. J.
CORPORATE SOURCE: Sir William Dunn Sch. Pathol., Univ. Oxford, Oxford, UK
SOURCE: Transplantation Proceedings (1985), 17(1, Book 2), 841-3
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rats, the infiltration of renal allografts by large nos. of mononuclear cells within a few days of grafting was not **prevented** by **treatment** with cyclosporine [**59865-13-3**] or by passive enhancement by **administration** of donor-specific alloantibody. However, cyclosporine and passive enhancement do appear to decrease the no. of infiltrating cells expressing the MRC OX8 antigen, i.e., cells with the cytotoxic-suppressor or natural-killer phenotypes. In contrast, cytotoxicity assays performed on target cells susceptible to natural killer cell-mediated lysis showed very similar levels of lytic activity irresp. of whether the effector cells were obtained from healthy **allografts** or those undergoing unmodified **rejection**. Apparently, **allograft rejection** in the rat is mediated by specific cytotoxic T cells rather than by nonspecific mechanisms. A difference in the phenotypes of cellular infiltrates between **treated** and untreated groups was obsd. which was assocd. with a difference in alloantigen-specific cytotoxic activity. Mononuclear cells harvested from passively enhanced grafts or grafts in recipients **treated** with cyclosporine showed min. ability to lyse concanavalin A-**treated** blasts, expressing the nonshared haplotype between donor and host, whereas cells from grafts from grafts in untreated recipients showed potent lytic activity.

L10 ANSWER 18 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:132305 HCAPLUS
DOCUMENT NUMBER: 100:132305
TITLE: Failure of cyclosporin-A to induce immunological unresponsiveness to nerve allografts
AUTHOR(S): Zalewski, Andrew A.; Gulati, Adarsh K.
CORPORATE SOURCE: Lab. Neurochem., Natl. Inst. Neurol. Commun. Disorders and Stroke, Bethesda, MD, 20205, USA
SOURCE: Experimental Neurology (1984), 83(3), 659-63
CODEN: EXNEAC; ISSN: 0014-4886
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although some allografts bearing major and minor transplantation antigens can survive after the cessation of immunosuppression with cyclosporin A (Cy-A) [**59865-13-3**], nerve allografts do not. In an attempt to induce immunol. unresponsivenss to nerve allografts, grafts contg. only minor transplantation antigens were used and the duration of Cy-A **therapy** was varied from 2 to 12 wk. Nerve allografts survived in rats during Cy-A **therapy**, but when the drug **administration** ceased, the **allografts** were **rejected**. Other factors besides the degree of histoincompatibility and duration of Cy-A **treatment** must be involved in detg. whether or not unresponsiveness develops to allografts after Cy-A withdrawal. Apparently, nerve allograft immunosuppression generated by Cy-A

requires regular **administration** of the drug.

L10 ANSWER 19 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:96371 HCAPLUS
DOCUMENT NUMBER: 100:96371
TITLE: Cyclosporin and experimental corneal transplantation
AUTHOR(S): Roussel, T. J.; Osato, M. S.; Wilhelmus, K. R.
CORPORATE SOURCE: Cullen Eye Inst., Baylor Coll. Med., Houston, TX, 77030, USA
SOURCE: Transplantation Proceedings (1983), 15(4, Suppl. 1-2), 3081-3
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following exptl. corneal transplantation in rabbits, ocular **treatment** with cyclosporin (I) [**59865-13-3**] (25 .mu.g/h, for 28 days) resulted in a delay in the onset of **graft rejection**. **Allograft rejection** in control animals rapidly proceeded to complete opacification of donor tissue, despite subsequent topical I **administration**. In the I-**treated** animals that subsequently rejected, the reinstitution of topical I at 500 .mu.g/h suppressed the reaction, and minimal progression was obsd. during the 7-day course of addnl. **therapy**. Although these corneas did not clear completely, translucency improved.

L10 ANSWER 20 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:96370 HCAPLUS
DOCUMENT NUMBER: 100:96370
TITLE: Cyclosporin prolongs skin allografts in a rat burn model
AUTHOR(S): Achauer, B. M.; Hewitt, C. W.; Black, K. S.; Philosophe, B.; Linfesty, R. L.; Furnas, D. W.
CORPORATE SOURCE: Div. Plast. Surg., Univ. California, Irvine, CA, 92717, USA
SOURCE: Transplantation Proceedings (1983), 15(4, Suppl. 1-2), 3073-6
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The median survival time of skin allografts in thermally injured rats was significantly increased by cyclosporin (I) [**59865-13-3**] (25 mg/kg/day, for 20 days) **treatment**. The thermally injured rats receiving I decreased in wt. during I **administration**. It did not appear that neutrophil function was affected in the I burn model, since neutrophil counts remained normal during the course of the investigation and the rats did not show an increased rate of bacterial infection. Thus, I is an effective immunosuppressant in **preventing** skin **allograft rejection** in a burn model.

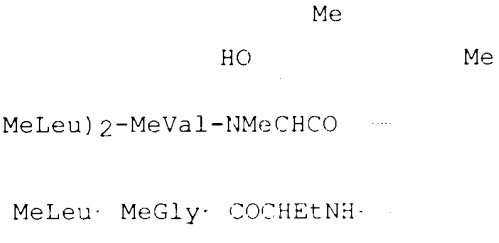
L10 ANSWER 21 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:96364 HCAPLUS
DOCUMENT NUMBER: 100:96364
TITLE: Successful small bowel allografts in piglets using cyclosporine
AUTHOR(S): Ricour, C.; Revillon, Y.; Arnaud-Battandier, F.;

Ghnassia, D.; Weyne, P.; Lauffenburger, A.; Jos, J.; Fontaine, J. L.; Gallix, P.; Vaiman, M.
CORPORATE SOURCE: Clin. Chir. Infant., Hop. Enfants Mal., Paris, F, 75730, Fr.
SOURCE: Transplantation Proceedings (1983), 15(4, Suppl. 1-2), 3019-26
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three groups of piglets with small bowel allografts were **treated** with cyclosporin A(I) [**59865-13-3**] (beginning 48 h before transplantation in both donor and recipient) according to the following protocol: (1) every other day i.m. at 25 mg/kg; (2) every day orally at the same dose; (3) every day i.v. at 8 mg/kg for 5-10 days, then orally 25 mg/kg. In piglets without I or when given every other day, **rejection** of the small bowel **allograft** occurred between 5 and 20 days. Subacute or delayed reactions were obsd. in 10 cases (14 enterostomies and 6 immediate end-to-end anastomosis) when I was given orally, and were probably due to malabsorption of the liposol. drug, as demonstrated by the null or below 250 ng/mL plasma I levels. The other 13 cases (3 immediate end-to-end anastomosis and venous I perfusion and 10 enterostomies) with perfect graft tolerance received a sufficient amt. of I, as shown by plasma I always >250 ng/mL. Thus, the **prevention** of the vicious circle of malabsorption-**rejection** and the success of intestinal **transplantation** depends on the venous path of **administration** of I, until intestinal transport returns to normal. Later, when oral ingestion is substituted for parenteral **administration**, it is necessary to control the plasma I levels by adapting the dose and way of **administration**.

L10 ANSWER 22 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:29411 HCAPLUS
DOCUMENT NUMBER: 100:29411
TITLE: Prolongation of rat kidney allografts by pretransplant administration of donor antigen extract or whole blood transfusion combined with a short course of cyclosporine
AUTHOR(S): Yasumura, Tadaki; Kahan, Barry D.
CORPORATE SOURCE: Med. Sch., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Transplantation (1983), 36(6), 603-9
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immunosuppressive effect of the combination of a 3-day course of cyclosporine [**59865-13-3**] with 1 i.v. injection of 3M KCl-extd. donor splenic antigen or donor blood transfusion was tested across the strong histocompatibility barrier causing **rejection** within 8 days of kidney **transplants** from Buffalo (Buf, RT1b) to Wistar-Furth (WFu, RT1a) inbred rats. **Administration** of 10 mg/kg/day cyclosporine alone for 3 days (-1, 0, and 1) slightly prolonged graft survival time from 7 to 11 days. The combination of cyclosporine with donor Buf 3M KCl antigen or with a Buf blood transfusions **administered** 1 day prior to transplantation caused greater prolongation of graft survival, 19 and 25 days, resp. Neither 3rd-party BN sol. antigen nor BN blood transfusions acted synergistically with cyclosporine to prolong Buf

graft survival. Increasing doses of donor-sol. antigen up to an optimal dose of 5 mg proportionately prolonged graft survival; however, **administration** of 10 mg antigen was less effective than 5 mg. On the other hand, **administration** of 1 mL of donor blood achieved the maximal effect. Lymphocytes harvested 10 days after transplantation from recipients that had received combined **therapy** with cyclosporine and donor 3M KCl antigen not only displayed specific unresponsiveness to donor stimulator cells in mixed lymphocyte culture, but also specifically suppressed the proliferative response of syngeneic, virgin WFu responder cells to allogeneic donor Buf but not to 3rd-party BN cells. Furthermore, suppressor cell activity was suggested by diminished responses in an in vivo local adoptive mixed lymphocyte culture assay and by prolongation of Buf kidney survival following systemic adoptive transfer. Apparently, immunosuppression with cyclosporine permits induction of specific suppressor cyclosporine permits induction of specific suppressor cells by 3M KCl donor antigen, resulting in specific unresponsiveness to allografts.

L10 ANSWER 23 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:447651 HCAPLUS
DOCUMENT NUMBER: 99:47651
TITLE: Transplantation of rat insulinoma allografts with cyclosporin A
AUTHOR(S): Cance, William G.; Vervaert, Carol; Seigler, H. F.
CORPORATE SOURCE: Med. Cent., Duke Univ., Durham, NC, USA
SOURCE: Surgery (St. Louis) (1983), 93(2), 279-88
CODEN: SURGAZ; ISSN: 0039-6060
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

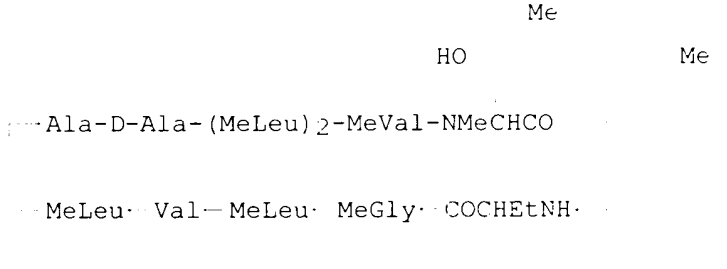


I

AB Cyclosporin A (I) [**59865-13-3**] was **administered** to Lewis rats i.p. for 21 days, beginning 1 day before s.c. KX insulinoma engraftment. Dosages of 8 and 12 mg/kg/day failed to suppress rejection, as no palpable tumor or blood glucose level changes were obsd. A dosage of 17 mg/kg/day allowed full allograft function without serious drug-related side effects in this short-term study. Blood glucose levels in the successfully engrafted recipients fell to an av. of 43 mg/dL. When I **treatment** was stopped, the insulinoma **allografts** were **rejected** within 14 days, suggesting that continued presence of the drug is necessary to maintain immunosuppression. Apparently, I can be **administered** as a single immunosuppressive agent to **prevent** early **rejection**

of insulinoma **transplanted** across a major histocompatibility barrier in the exptl. animal.

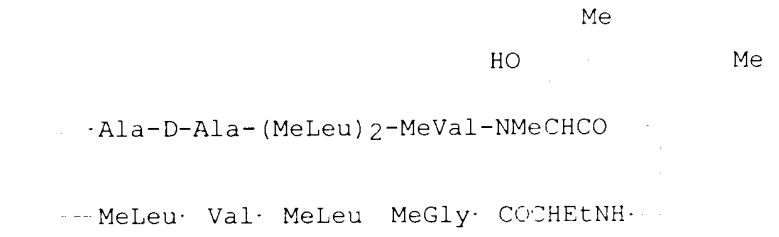
L10 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:191457 HCAPLUS
DOCUMENT NUMBER: 98:191457
TITLE: Reduced sensitization risk in pregraft cyclosporin-A/blood-transfusion-enhanced rabbit skin allografts
AUTHOR(S): Dumble, L. J.; King, H. P.; Clunie, G. J. A.; Bowes, L. G.; Judson, R. T.
CORPORATE SOURCE: Dep. Surg., R. Melbourne Hosp., Parkville, 3050, Australia
SOURCE: Transplantation Proceedings (1983), 15(1, Book 2), 1000-2
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB The mean skin allograft survival time in untreated rabbits was 7.1 days, pregraft cyclosporin A (I) [**59865-13-3**] (20 mg/kg i.m. 7 days pregraft), peroperative I (20 mg/kg), and peroperative blood transfusion significantly extended mean allograft survival times to 9.3, 12.5, and 11.1 days, resp. **Pregraft** transfusion resulted in accelerated **rejection**, presumably due to sensitization, in at least 2 of the 8 animals. Simultaneous **administration** of donor blood and I pregraft resulted in prolongation of **graft** survival without evidence of accelerated **rejection**; the mean survival time was 14.1 days. Peroperative blood transfusion and I **treatment** gave a greater extension of the mean survival time (28.8 days). Thus, simultaneous I and blood-transfusion may have an important place in the pregraft conditioning of potential allograft recipients.

L10 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:46632 HCAPLUS
DOCUMENT NUMBER: 98:46632
TITLE: The influence of cyclosporin A on experimental autoimmune thyroid disease in the rat
AUTHOR(S): McGregor, A. M.; Rennie, D. P.; Weetman, A. P.; Hassman, R. A.; Foord, S. M.; Dieguez, C.; Hall, R.
CORPORATE SOURCE: Dep. Med., Welsh Natl. Sch. Med., Cardiff, CF4 4XN, UK
SOURCE: Life Sciences (1983), 32(1-2), 97-108

CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB Female PVG/c rats, thymectomized on weaning and given 4 courses of whole body irradn. to a total dose of 1000 rads, developed exptl. **autoimmune** thyroid **disease** (EAITD) as assessed by histol. evidence of thyroiditis and circulating levels of antithyroglobulin antibodies. Hypothyroidism resulted, and induction of the disease was assocd. with a highly significant fall in T-lymphocyte nos. Eight wk after their last dose of irradn., the animals commenced **treatment** with cyclosporin A (I) [**59865-13-3**] (10 mg/kg rat/day, intragastrically) and were **treated** for varying time intervals thereafter. The reversal of the T-lymphocyte helper: suppressor ratio on Cyclosporin A **therapy** was assocd. with a significant improvement in the disease process. The alterations in the T cell subsets and in the disease lasted only as long as the drug was **administered** and thereafter reverted towards that seen in the control groups of animals receiving no **treatment**.

L10 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:27507 HCAPLUS
DOCUMENT NUMBER: 98:27507
TITLE: Effect of cyclosporin A on spontaneous autoimmune thyroiditis of obese strain (OS) chickens
AUTHOR(S): Wick, Georg; Mueller, Pia Ulrike; Schwarz, Siegfried
CORPORATE SOURCE: Med. Sch., Univ. Innsbruck, Innsbruck, A-6020, Austria
SOURCE: European Journal of Immunology (1982), 12(10), 877-81
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

Me

HO Me

·Ala-D-Ala-(MeLeu)2-MeVal-NMeCHCO

MeLeu· Val· MeLeu· MeGly· COCHEtNH· I

AB cyclosporin A (I) [**59865-13-3**] oral **administration** to chickens with skin allografts induced immunosuppressive effects in that it prolonged the skin allograft survival when compared to untreated controls. I **administration** (posthatching) to obese strain (OS) chickens with spontaneous autoimmune thyroiditis (SAT) did not alter the frequency and severity of the disease or alter the prodn. of thyroglobulin autoantibodies (Tg-AAb). **Treatment** of OS embryos on days 15, 17, and 19 of incubation caused more severe SAT and higher titers and frequency of Tg-AAb as compared to untreated controls. The role of cytotoxic T cells in the initial phases of SAT is discussed. I may not be the drug of choice for the **treatment** of at least some **autoimmune diseases**.

L10 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:11202 HCAPLUS
DOCUMENT NUMBER: 98:11202
TITLE: Immunosuppression of rabbit ovarian and adnexal allografts with cyclosporin A
AUTHOR(S): Green, C. J.; Grimaldi, G.; Simpkin, S.; Johnson, A.
CORPORATE SOURCE: Div. Comparative Med., MRC Clin. Res. Cent., Harrow/Middx., UK
SOURCE: Cyclosporin A, Proc. Int. Conf. (1982), Meeting Date 1981, 165-71. Editor(s): White, David, J. G. Elsevier Biomed.: Amsterdam, Neth. CODEN: 48WDAP
DOCUMENT TYPE: Conference
LANGUAGE: English
AB In rabbits, ovaries and their oviducts were rejected as vigorously as other tissues when transplanted between immunol. incompatible animals. A short course of **treatment** with cyclosporin A (I) [**59865-13-3**] was highly effective in **preventing** rejection. Only 2 ovaries of 20 **allografts** showed signs of **rejection**, even though in some cases they were examd. as long as 4 mo after stopping **administration** of I. There was no evidence to suggest that follicle formation and ovulation were depressed by I. In fact, normal offspring were produced by 1 recipient of an ovarian allograft.

L10 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:11200 HCAPLUS
DOCUMENT NUMBER: 98:11200
TITLE: Experimental lung transplantation with

cyclosporin A
AUTHOR(S): Veith, Frank J.; Norin, Allen J.; Emeson, Eugene; Pinsker, Kenneth L.; Kamholz, Stephan L.
CORPORATE SOURCE: Albert Einstein Coll. Med., Montefiore Hosp., New York, NY, 10467, USA
SOURCE: Cyclosporin A, Proc. Int. Conf. (1982), Meeting Date 1981, 143-54. Editor(s): White, David, J. G. Elsevier Biomed.: Amsterdam, Neth.
CODEN: 48WDAP
DOCUMENT TYPE: Conference
LANGUAGE: English
AB In dogs, daily **administration** of cyclosporin A (I) [**59865-13-3**] combined with 14 days of low-dose azathioprine [446-86-6] **treatment** provided the most effective immunosuppression yet available for use in lung transplantation. Lung **allograft rejection** was completely obviated, without the need for any corticosteroids, for >5 mo in 2 of the 5 animals so **treated**, whereas in the remaining 3 dogs rejection was controlled with corticosteroids. However, immunosuppression from I was not always perfect. Within 2 mo of **transplantation**, some evidence of **rejection** occurred in approx. half of the animals **treated**. This rejection was not completely **prevented** when other agents were added to the I and azathioprine or replaced the latter drug. Prophylactic **administration** of corticosteroids was assocd. with a higher incidence of infection, failed to **prevent** rejection, and appeared to worsen overall results. The **rejection** of the lung **allografts** of animals receiving I differed from that obsd. in animals receiving std. immunosuppression.

L10 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:607954 HCAPLUS
DOCUMENT NUMBER: 97:207954
TITLE: Antigen dependence of cyclosporin A-induced allograft acceptance
AUTHOR(S): Kasahara, Kogoro; White, David J. G.; Calne, Roy Y.
CORPORATE SOURCE: Dep. Surg., Addenbrooke's Hosp., UK
SOURCE: Transplantation (1982), 34(4), 216-18
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB cyclosporin A (I) [**59865-13-3**] (15 mg/kg/kg/day for 14 days) induced the acceptance of a heart transplant in rats which persisted even after discontinuation of I **administration**. A second heart transplant after discontinuation of I **therapy** was also accepted, indicating a systemic effect of I which persists after discontinuation of I **therapy**. This acceptance-inducing effect failed to persist in animals from which the organ transplant was removed after discontinuation of I **therapy**; subsequent (4 wk) heart **transplants** were **rejected**. Apparently, the acceptance induced by I is a dynamic phenomenon, requiring the presence of the donor antigen, but not the continued **administration** of I.

L10 ANSWER 30 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:538336 HCAPLUS

DOCUMENT NUMBER: 97:138336
TITLE: Effect of cyclosporin A on the in situ inflammatory response of human renal allograft rejection. A preliminary report
AUTHOR(S): Hayry, Pekka; Ahonen, J.; Von Willebrand, E.; Eklund, B.; Hockekstedt, K.; Kauste, A.; Taskinen, E.; Lautenschlager, I.; Lalla, M.; Sarelin, H.
CORPORATE SOURCE: Fourth Dep. Surg., Univ. Helsinki, Helsinki, Finland
SOURCE: Scandinavian Journal of Immunology (1982), 16(2), 135-49
CODEN: SJIMAX; ISSN: 0300-9475
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Twenty cadaveric kidney allograft recipients were prerandomized into 2 groups. Ten patients (control group) were **treated** postoperatively with azathioprine (AZA) [446-86-6] plus methylprednisolone (MP) [83-43-2]; the other 10 received cyclosporin A (CyA) [**59865-13-3**] as the only immunosuppressive agent. Both groups received MP during rejection. Some patients **treated** with CyA had a significant initial decrease in urine output, reaching control values approx. 1 wk postoperatively. The mechanism behind this deteriorated renal function is not clear, but it seemed to have been caused by injuries to the kidney tubular component, since a distinct monocytic-lymphocytic inflammation and severe cytol. changes resembling pronounced acute tubular necrosis were obsd. concomitantly in transplant aspiration cytol. The CyA-**treated** patients had normal levels of blood leukocytes, thrombocytes, and lymphocytes but displayed a strong early blood eosinophilia that was absent in the control subjects. During the first 30 days after transplantation, 15 in situ episodes of inflammation were recorded in the 9 transplants **treated** with CyA, whereas only 6 episodes were found in the 10 transplants receiving AZA + MP. The first inflammatory episode in the CyA-**treated** transplants peaked between days 5 and 8 after transplantation and was followed by another distinct inflammatory episode between days 23 and 26. In the AZA- plus MP-**treated** transplants, only one inflammation episode was obsd., with a peak on day 14 postoperatively. The inflammatory cell types most prominently present in the CyA-**treated** transplants were lymphocytes, B plasmablasts, and monocytes. The early inflammatory episodes in the CyA-**treated** transplants may have been related to the fact that during the initial i.m. **administration**, **therapeutic** CyA concns. in patient serum were not achieved until the fourth postoperative day during peroral **administration**. The onset of transplant function had no impact on the in situ inflammatory response of **rejection** in the CyA-**treated transplants** or on the concn. of CyA in patient serum. Apparently, CyA may also be used in initially nonfunctioning transplants. The major histocompatibility complex (MHC) antigens on the healthy grafts **treated** with AZA plus MP was not demonstrated. However, in healthy allografts **treated** with CyA, both classes of MHC antigens were nearly invariably demonstrable on the graft endothelial cell surface. Approx. 60% allograft survivals were recorded in both groups at 6 mo, and all patients with functioning

grafts were able to work.

L10 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:538328 HCAPLUS
DOCUMENT NUMBER: 97:138328
TITLE: Cyclosporin A for immunosuppression: observations in rat heart, pancreas, and islet allograft models and in human renal and pancreas transplantation
AUTHOR(S): Rynasiewicz, John J.; Sutherland, David E. R.; Ferguson, Ronald M.; Squifflet, Jean Paul; Morrow, Charles E.; Goetz, Frederick C.; Najarian, John S.
CORPORATE SOURCE: Health Sci. Cent., Univ. Minnesota, Minneapolis, MN, USA
SOURCE: Diabetes (1982), 31(Suppl. 4), 92-108
CODEN: DIAEAZ; ISSN: 0012-1797
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Low-dose cyclosporin A (I) [**59865-13-3**] was tested in various combinations with low-dose prednisone [53-03-2], azathioprine [446-86-6], or total lymphoid irradn. in rat heart, pancreas, and islet allograft models. Several combinations were synergistic and when **administered** continuously indefinitely **prevented rejection** of heart **allografts**, but only delayed **rejection** of pancreatic **allografts transplanted** across a major histocompatibility barrier. I by itself prolonged the survival of islet allografts transplanted across a minor, but not a major, histocompatibility barrier. I and azathioprine had a synergistic effect in the minor histocompatibility barrier islet transplant model, but, in the nontoxic combinations tested, could not **prevent** rejection indefinitely. Preliminary results of a randomized prospective trial comparing I and low-dose prednisone vs. conventional immunosuppression in renal allotransplantation are presented. The use of I for clin. pancreas allotransplantation is also described.

L10 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:400439 HCAPLUS
DOCUMENT NUMBER: 97:439
TITLE: Rabbit corneal allograft survival following topical administration of cyclosporin A
AUTHOR(S): Kana, Jan S.; Hoffmann, Friedrich; Buchen, Renate; Krolik, Astrid; Wiederholt, Michael
CORPORATE SOURCE: Dep. Clin. Physiol., Freie Univ., Berlin, 1000/45, Fed. Rep. Ger.
SOURCE: Investigative Ophthalmology & Visual Science (1982), 22(5), 686-90
CODEN: IOVSDA; ISSN: 0146-0404
DOCUMENT TYPE: Journal
LANGUAGE: English
AB cyclosporin A (CS-A) [**59865-13-3**], selectively inhibiting cellular immunity, delayed the skin **graft**-induced **rejection** of corneal **allografts** in rabbits when **administered** subconjunctivally at 3 mg/kg/day or in the form of 5% water-sol. drops 5 times daily for 28 days. The

subconjunctival application of CS-A was irritating, whereas the topical instillation of the water-sol. prepn. was well tolerated. The corneal **grafts** were **rejected** after discontinuation of the **therapy**. Rejection was confirmed by scanning and transmission electron microscopy. The mechanisms by which CS-A delayed corneal **graft rejection** seems to depend mainly on the specific and/or the nonspecific effect of topical CS-A on lymphocytes.

L10 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:28382 HCAPLUS
DOCUMENT NUMBER: 96:28382
TITLE: Improved survival of transplanted lungs in mongrel dogs treated with cyclosporin A
AUTHOR(S): Norin, Allen J.; Veith, Frank J.; Emeson, Eugene E.; Montefusco, Cheryl M.; Pinsker, Kenneth L.; Kamholz, Stephan L.
CORPORATE SOURCE: Montefiore Hosp., Albert Einstein Coll., New York, NY, 10467, USA
SOURCE: Transplantation (1981), 32(3), 259-60
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In dogs with lung allografts, and **administration** of cyclosporin A [**59865-13-3**] (17, 13, and 9 mg/kg/day for the 1st 35 days, the next 65 days, and subsequent days, resp.) gave good results in **preventing** or controlling **transplant rejection** phenomena. Addnl. **therapy** with corticosteroids was necessary in some cases to maintain nearly normal lung structure and function. None of the severe side effects (lymphoma, hepato- and nephrotoxicity, and infection) sometimes reported with the use of cyclosporin A in organ transplantation was obsd.

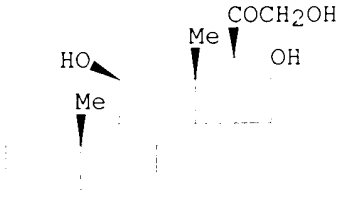
L10 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:562103 HCAPLUS
DOCUMENT NUMBER: 95:162103
TITLE: Suppression of corneal allograft rejection by cyclosporin A
AUTHOR(S): Salisbury, John D.; Gebhardt, Bryan M.
CORPORATE SOURCE: Eye Cent., Louisiana State Univ., New Orleans, LA, 70112, USA
SOURCE: Archives of Ophthalmology (Chicago, IL, United States) (1981), 99(9), 1640-3
CODEN: AROPAW; ISSN: 0003-9950
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclosporin A (I) [**59865-13-3**] (5, 10, or 20 mg, retrobulbar) **administration** significantly prolonged corneal allograft survival in rabbits. All **allografts** in untreated eyes were **rejected** within 40 days. More than 40% of cornea allografts in **treated** eyes survived >70 days. The suppression of host rejection response by I was dose-dependent. I was less effective in suppressing **allograft rejection** in heavily vascularized, inflamed **graft** sites. No adverse side effects were seen when I was injected locally into the rabbit eye. Thus, I is a safe, potent immunosuppressive agent in this model.

L10 ANSWER 35 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:508765 HCAPLUS
DOCUMENT NUMBER: 95:108765
TITLE: Cyclosporin A spares selectively lymphocytes with donor-specific suppressor characteristics
AUTHOR(S): Hutchinson, Ian F.; Shadur, Craig A.; Duarte, J. S. Alberto; Strom, Terry B.; Tilney, Nicholas L.
CORPORATE SOURCE: Brigham and Women's Hosp., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Transplantation (1981), 32(3), 210-16
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of cyclosporin A (Cy A) [**59865-13-3**] on the host responses to heart allografts was examd. in rats following **administration** of the drug for 7 days after grafting. All **grafts** functioned > 100 days without **rejection** episodes in animals of major histocompatibility differences. Thymic or splenic lymphocytes (1 .times. 108) from LEW recipients of (LEW .times. BN)F1 hearts were transferred at varying periods into untreated LEW rats transplanted with (LEW .times. BN)F1 test hearts 24 h later. Test grafts survived 12 to 16 days significantly longer than in untreated animals. Cells from normal LEW animals, Cy A-**treated** but ungrafted, and grafted but not **treated** animals, all failed to prolong test graft survival. Specificity of the effect was tested in vivo, using hearts from donor and third-party rats, and in vitro, using the mixed lymphocyte response (MLR). In vivo, thymocytes from **treated** LEW recipients of (LEW .times. WF)F1 grafts failed to prolong (LEW .times. BN)F1 test grafts; conversely, transferred thymocytes from LEW recipients of (LEW .times. BN)F1 grafts failed to prolong (LEW .times. WF)F1 grafts. The MLR of lymphocytes from Cy A-**treated** rats was significantly decreased against donor lymphocytes but not against third-party lymphocytes. Addnl., both cellular and humoral immunity mounted by Cy A-**treated** recipients was depressed throughout the entire follow-up period. Prolonged heart graft survival after 7 days of Cy A **treatment** suggests emergence of cells with specific suppressor activity, which in turn may cause profound abrogation of host effector responses against vascularized organ allografts.

L10 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:537937 HCAPLUS
DOCUMENT NUMBER: 93:137937
TITLE: Cyclosporin A prolongation of segmental pancreatic and islet allograft function in rats
AUTHOR(S): Rynasiewicz, J. J.; Sutherland, D. E. R.; Kawahara, K.; Gorecki, P.; Najarian, J. S.
CORPORATE SOURCE: Health Sci. Cent., Univ. Minnesota, Minneapolis, MN, USA
SOURCE: Transplantation Proceedings (1980), 12(2), 270-4
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A formulation of cyclosporin A (I) [**59865-13-3**] in an Intralipid-EtOH vehicle provided effective immunosuppression. A min. dose of I that completely **prevented** rejection when

dissolved in this vehicle and **administered** i.p. was 1/2 the effective gavage dose of I formulated in Tween 80-EtOH. Rats receiving I i.p. appeared much healthier than those receiving gavage. The peritoneal cavity of i.p. injected rats at interval laparotomy or autopsy showed no evidence of drug pptn. or adhesion formation. I **administered** i.v. (Intralipid-EtOH) for the 1st 4 posttransplant days followed by gavage **administration** resulted in only 1 **allograft rejection** over the period of observation. I thus may provide more adequate immunosuppression and eliminate the need for diabetogenic agents.

L10 ANSWER 37 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:526124 HCAPLUS
DOCUMENT NUMBER: 93:126124
TITLE: Detrimental effect of steroids on cyclosporin-A-induced prolonged allograft survival
AUTHOR(S): Dunn, D. C.; White, D. J. G.; Herbertson, B. M.; Rolles, K.
CORPORATE SOURCE: Surg. Dep., Addenbrooke's Hosp., Cambridge, CB2 2QQ, UK
SOURCE: Transplantation Proceedings (1980), 12(2), 335-8
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB In rabbits with kidney allografts, 23 unmodified **allograft** recipients died of **rejection** in 11.4 days. Histologic changes consisted of marked or severe mononuclear cell infiltration, marked arterial lesions, and destruction of renal tubules. Six grafts also showed evidence of acute tubular necrosis. Twelve animals given cyclosporin A (I) [**59865-13-3**] alone survived to a mean of 61.3 days. The addn. of 6-methylprednisolone (II) [6923-42-8] caused a marked deterioration in the survival achieved after **treatment** with I alone. The mean survival was decreased to 27.7 days compared to 61.3 days for animals **treated** with I only. There were 6 deaths before 15 days in I plus II-**treated** animals and only 2 in I only **treated** animals. None of the 12 animals **treated** with I alone died with sepsis, whereas 5 of 11 of the animals **treated** with both I and II had this complication. There were no long surviving animals in the I + II **treated** group, all animals died within 69 days. In contrast, in the group

treated with I alone, almost half the animals survived beyond 80 days. Thus, I given alone increases survival of kidney allograft recipients more effectively than when **administered** in combination with II.

L10 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:553 HCAPLUS
DOCUMENT NUMBER: 92:553
TITLE: Prolongation of allograft survival by cyclosporin A
AUTHOR(S): Cosimi, A. Benedict; Shield, Charles F.; Peters, Charles; Burton, Robert C.; Scott, Gregory; Russell, Paul S.
CORPORATE SOURCE: Gen. Surg. Serv., Massachusetts Gen. Hosp., Boston, MA, USA
SOURCE: Surgical Forum (1979), 30, 287-9
CODEN: SUFOAX; ISSN: 0071-8041
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Survival of first-set H-2 incompatible murine skin allografts was prolonged to 20 days (control 13.5) by **treatment** with cyclosporin A (I) [**59865-13-3**] at 75 mg/kg/day for 14 days and further prolonged to 26 days by a dosage of 150 mg/kg **administered** 3 times/wk until the time of rejection. Attempts to increase the dosage further resulted in unacceptable toxicity. Immunosuppression with rabbit antimouse thymocyte globulin (RATG) in this donor-recipient combination regularly provided a mean skin allograft survival of 24-28 days. **Treatment** with I (25 mg/kg/day for 14 days) also prolonged the survival to 20-26 days (control 8-10 days) of rhesus monkeys with renal allografts. Survival of recipient monkeys **treated** with horse anti-human thymocyte globulin was prolonged to 30-70 days with all monkeys eventually dying of uremia secondary to **allograft rejection**. Nonspecific depression of mixed lymphocyte cultures after **treatment** with I was obsd. Thus, I is a nonspecific suppressor of cell-mediated immunity and **allograft rejection** with valuable clin. potential.

L10 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1979:449501 HCAPLUS
DOCUMENT NUMBER: 91:49501
TITLE: Prolongation of mouse skin allograft survival by cyclosporin A: graft rejection after withdrawal of therapy
AUTHOR(S): Lems, S. P. M.; Koene, R. A. P.
CORPORATE SOURCE: Dep. Med., Sint Radboud Hosp., Nijmegen, Neth.
SOURCE: IRCS Medical Science: Library Compendium (1979), 7(4), 184
CODEN: IRLCDZ; ISSN: 0305-6651
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Daily oral **administration** of cyclosporin A [**59865-13-3**] to mice **prevented** the **rejection** of skin **grafts** made across a major histocompatibility barrier. Although all grafts survived during **treatment** with this immunosuppressant for .apprx.50 days, **graft rejection** occurred on cessation of the

cyclosporin A **treatment**. The time period between withdrawal of **treatment** and **rejection** of the **grafts** (10-13 days) was approx. the same as the graft survival time in untreated animals.

E1 THROUGH E1 ASSIGNED

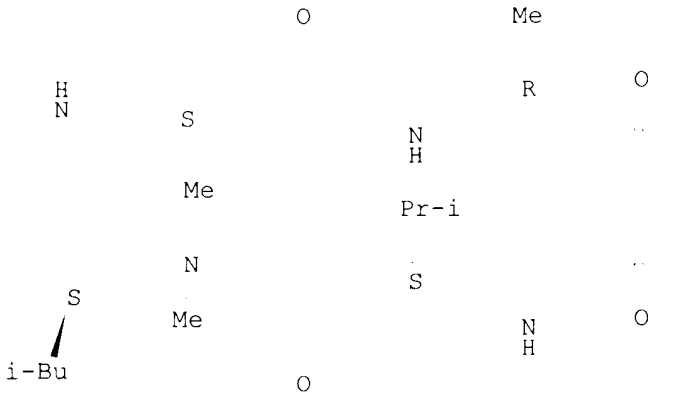
FILE 'REGISTRY' ENTERED AT 11:17:04 ON 08 JAN 2003
L11 1 SEA FILE=REGISTRY ABB=ON PLU=ON 59865-13-3/BI

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **59865-13-3** REGISTRY
CN Cyclosporin A (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
OTHER NAMES:
CN 7: PN: WO0002548 PAGE: 30 claimed protein
CN Antibiotic S 7481F1
CN Ciclosporin
CN Cipol N
CN Consupren
CN Cyclosporin
CN Cyclosporine
CN Cyclosporine A
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl]
CN Neoplanta
CN Neoral
CN OL 27-400
CN Ramihyphin A
CN S-Neoral
CN Sandimmun
CN Sandimmun Neoral
CN Sandimmune
CN Sang-35
CN SangCyA
CN SDZ-OXL 400
CI COM
SQL 11

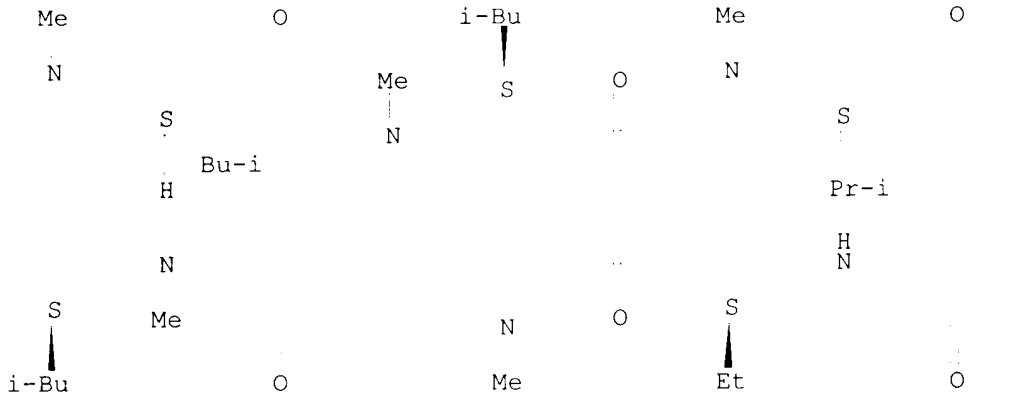
SEQ 1 XXXLVLAALL V

Absolute stereochemistry.
Double bond geometry as shown.

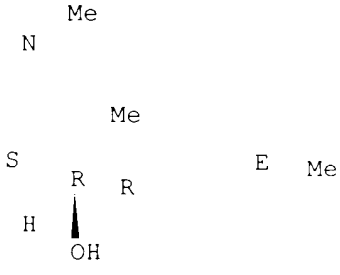
PAGE 1-A



PAGE 1-B



PAGE 1-C



Searcher : Shears 308-4994

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 138:13493

REFERENCE 2: 138:12504

REFERENCE 3: 138:12369

REFERENCE 4: 138:12359

REFERENCE 5: 138:11574

REFERENCE 6: 138:11246

REFERENCE 7: 138:11238

REFERENCE 8: 138:11234

REFERENCE 9: 138:11232

REFERENCE 10: 138:11218

FILE 'CAOLD' ENTERED AT 11:18:35 ON 08 JAN 2003
L12 0 S L11

FILE 'USPATFULL' ENTERED AT 11:18:50 ON 08 JAN 2003
L11 1 SEA FILE=REGISTRY ABB=ON PLU=ON 59865-13-3/BI
L13 652 SEA FILE=USPATFULL ABB=ON PLU=ON L11
L14 0 SEA FILE=USPATFULL ABB=ON PLU=ON L13(L)ADMIN?

L11 1 SEA FILE=REGISTRY ABB=ON PLU=ON 59865-13-3/BI
L13 652 SEA FILE=USPATFULL ABB=ON PLU=ON L11
L15 0 SEA FILE=USPATFULL ABB=ON PLU=ON L13(L)(TREAT? OR THERAP? OR PREVENT?)

L11 1 SEA FILE=REGISTRY ABB=ON PLU=ON 59865-13-3/BI
L13 652 SEA FILE=USPATFULL ABB=ON PLU=ON L11
L21 0 SEA FILE=USPATFULL ABB=ON PLU=ON L13(L)((?TRANSPLANT? OR ?GRAFT?)(5A)REJECT? OR (AUTOIMMUN? OR AUTO IMMUN?)(5A)(DISEAS? OR DISORDER) OR (CONICAL OR EPITHEL?)(W)CORNEA# OR KERATIT? OR LEU!OMA OR MOOREN?(1W)ULCER OR SCLEVIT? OR GRAVE?(1W)OPHTHALMOPATH?)

FILE 'HOME' ENTERED AT 11:25:33 ON 08 JAN 2003